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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P36154A/EBA/BOU	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2005/000518	International filing date *(day/month/year)* 14.02.2005	Priority date *(day/month/year)* 12.02.2004

International Patent Classification (IPC) or national classification and IPC
INV. C12N5/06

Applicant
UNIVERSITY OF NEWCASTLE UPON TYNE et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.01.2006	28.03.2006

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/000518

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-37	as originally filed

Sequence listings part of the description, Pages

1-3	as originally filed

Claims, Numbers

1-13	received on 30.01.2006 with letter of 26.01.2006

Drawings, Sheets

1/8-8/8	as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 5-13

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 5-13

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-4 .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-4
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-4
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item I

Basis of the report

1. The amendments filed with the letter of 26.01.2006 are formally allowable under Article 34(2)(b) PCT because they do not introduce subject-matter extending beyond the content of the application as filed.

Re Item II

Priority

1. The present application validly claims priority from 12.02.2004. Any documents cited in the International Search Report as P documents have therefore not been considered as comprised in the prior art relevant for the present application.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. No meaningful examination could be performed for new claims 5-13, for the following reason:
   No complete international search report has been established for said claims, corresponding to original claims 10-14, 22 and 17-19 (see Form PCT/ISA/210). Accordingly, said claims need not be the subject of international preliminary examination (Rule 66. 1.(e) (PCT)).

Re Item IV

Lack of unity of invention

1. The IPEA agrees with the objection put forward by the ISA as to lack of unity pursuant to Rule 13 PCT, and considers that the present invention (new claims 1-13)

relates to three distinct groups of inventions. New claims 1-13 correspond to original claims 6-14, 22 and 17-19, which belong to three distinct groups of inventions (groups I, II and III) for the reasons outlined in Form PCT/ISA/210.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: RICHARDS M et al.: "Human feeders support prolonged undifferentiated growth of human inner cell masses and embryonic stem cells" NATURE BIOTECHNOLOGY, vol. 20, no. 9, September 2002, pages 933-936

D2: HOVATTA O et al.: "A culture system using human foreskin fibroblasts as feeder cells allows production of human embryonic stem cells." HUMAN REPRODUCTION, vol. 18, no. 7, July 2003 (2003-07), pages 1404-1409,

D3: HENDERSON J K et al.: "Preimplantation human embryos and embryonic stem cells show comparable expression of stage-specific embryonic antigens." STEM CELLS 2002, vol. 20, no. 4, 2002, pages 329-337,

2. **Novelty and Inventive step** (Article 33(2) and (3) PCT)

2.1. The present application (Invention I, new claims 1-4) discloses the human embryonic stem cell line hES-NCL1, a stem cell bank comprising it and methods for screening agents for toxicity using it.

2.2. **D1** is a publication disclosing the derivation of a new human ES cell line with the Oct-4, SSEA-4, Tra1-60 and GCTM-2 phenotype.
D2 is a publication disclosing the culture of huES cells on human foreskin fibroblasts, having the Oct-4, SSEA-4, Tra1-60 phenotype.
D3 is a publication disclosing that huES cells express SSEA3, SSEA4, TRA-1-60, Oct-4 and Rex1.

2.3. None of the available prior art discloses the specific deposited cell-line of new claim 1. Said claim as well as claims 2-4 referring to it are thus considered novel and

inventive under the terms of Articles 33(2) and (3) PCT.

3. **Industrial applicability** (Article 33(4) PCT)
The subject-matter of the claims for which an opinion has been established (see item III) appears to be industrially applicable under the terms of Article 33(4) PCT.

Re Item VIII

Certain observations on the international application

1. Applicant's attention is drawn to the fact that, upon entry into the regional phase, patentability of claims relating to human embryos may underlie restrictions based on moral grounds. The EPO, for example, does not recognize as patentable the subject-matter of claims to the cloning of human beings, the modification of the germ line identity of human beings and the use of human embryos for industrial or commercial purposes (Article 53(a) and Rule 23d EPC). Claims to human embryonic stem cells might be regarded as falling under said exclusions.

Claims

1. The stem cell line hES-NCL1 deposited at NIBSC under Accession No. P-05-001.

2. An embryonic stem cell bank comprising a multiplicity of genetically distinct stem cell lines, including the stem cell line as claimed in Claim 1.

3. A method of screening an agent for toxicity and/or for therapeutic efficacy, said method comprising:

i. exposing the stem cell line as claimed in Claim 1 to said agent;

ii. monitoring any alteration in viability and/or metabolism of said stem cells; and

iii. determining any toxic or therapeutic effect of said agent.

4. A method of screening an agent for toxicity and/or for therapeutic efficacy, said method comprising:

i. exposing an embryonic stem cell bank as claimed in Claim 2 to said agent;

ii. monitoring any alteration in viability and/or metabolism of said stem cells; and

iii. determining any toxic or therapeutic effect of said agent.

5. A method of producing fibroblast-like cells, said method comprising:

i. providing the stem cell line as claimed in Claim 1;

ii. allowing cells of said stem cell line to differentiate into stem cell derived fibroblast-like cells.

6. The method of Claim 5 which is conducted without use of a specific stimulant for differentiation.

7. The method as claimed in either one of Claims 5 and 6 wherein the fibroblast-like cells are produced for a therapeutic purpose.

8. A method of culturing cells wherein the fibroblast-like cells obtained as claimed in Claims 5 or 6 act as feeder cells or condition cell culture media used during culture of the cells.

9. The method as claimed in Claim 8 wherein the cells being cultured are stem cells.

10. A self-feeder system for the growth of undifferentiated stem cells, said system comprising:

i. culturing the stem cell line as claimed in Claim 1; and

ii. allowing some of the cells of said stem cell line to differentiate into stem

cell derived fibroblast-like cells whilst the remainder of the cells of said embryonic stem cell line remain in an undifferentiated pluripotent, multipotent or unipotent state, whereby said stem cell derived fibroblast-like cells act as autogeneic feeder cells for said stem cells.

11. The fibroblast-like cell line hESCdF-NCL as deposited at ECACC under Accession No. 04010601.

12. A method of culturing cells wherein hESCdF-NCL cells act as feeder cells or condition cell culture media used during culture of the cells.

13. The method as claimed in Claim 12 wherein the cells being cultured are stem cells.